Title: NEUROPATHOLOGIC EFFECTS OF ANESTHETICS USED TO STOP STATUS EPILEPTICUS IN RATS

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Introduction: General anesthesia has been recommended when status epilepticus is refractory to conventional anticonvulsant therapy(1). However, there is no experimental basis for the selection of any particular anesthetic to stop seizures. We assessed the electrographic efficacy and delayed neuropathologic effects of four classes of anesthetics used to stop drug-induced seizures in rats.

Methods: Long-Evans Rats, 300-400 gms were fed ad lib. Anesthesia was induced in 3-4% halothane in oxygen followed by curare 0.6 mg IM, endotracheal intubation, and mechanical ventilation. The tail artery and right internal jugular vein were cannulated, 100 U of heparin was administered SQ, and erectal temperature probe and EEG electrodes were inserted. Halothane was discontinued for 60 minutes during which time 50% nitrous oxide and oxygen was given. Phenoxybenzamine, 0.05 mg was given IV followed by IV administration of the glutamate decarboxylase inhibitor(1), 3-mercaptopropionic acid (MPA), 0.475 mMol/kg. At the first sign of seizure activity, nitrous oxide was discontinued. With the onset of seizures hypertension was controlled by blood withdrawal into a heparinized syringe. Atropine .02 mg IV was given IV followed by .1 mg SQ qlh. Seizures were allowed to occur for 30 minutes. The method by which seizures were stopped defined the experimental group. There were five experimental groups with 4 rats in each group: (1)**Control:** 15 mg/kg thiopental IV bolus followed by 2-3 hours mechanical ventilation with 50% nitrous oxide, (2)**Thiopental:** 27 mg/kg IV followed by 20.9 mg/kg/hr for 2 hours, (3)**Isoflurane:** 4% inspired for 1 minute followed by 1-2% inspired for 2 hours titrated to maintain mean arterial blood pressure >60 mmHg, (4)**Ketamine:** 33.0 mg/kg IV followed by 9.12 mg/kg/hour for 2 hours, (5)**Midazolam:** 25 mg/kg IV followed by 9.7 mg/kg/hour for 2 hours. N20/02 50/50 was given for 2 hours after seizures in the control group and for 30-60 minutes after discontinuation of isoflurane in the isoflurane group. After two hours of anesthetic administration, vascular cannulae were removed, wounds closed, neostigmine 25 micrgm IV given and, with evidence of spontaneous respiration, animals extubated and allowed to recover for 3 days. At the end of this time cerebral perfusion fixation was performed with formaldehyde - acetic acid - methanol (8:1:1) followed by light microscopic examination. On serial coronal sections the substantia nigra was assessed. In the section with maximal damage, cross-sectional areas of substantia nigra sponginess were measured. (Prior experiments with this seizure model demonstrated substantia nigra sponginess, the extent of which correlated with seizure duration.) The following physiologic variables were maintained pre and post-seizures: pHa 7.3-7.5, paC02 25-40 mmHg, pa02 > than 100 mmHg, MAP > 60 mmHg; during seizures: pHa 7.2-7.4 paC02 30-50 mmHg, MAP 100-150 mmHg, and pa02 > 100 mmHg. Area of substantia nigra damage in each group was compared to controls with students one-tailed T test.

Results: All control and treated rats survived the 3-day post seizure period. In every rat given an anesthetic, seizures stopped promptly. The maximal oval area of substantia nigra sponginess in each group follows (sq mm) (mean + sem): Control 3.44+.56, ketamine 2.47+.97, midazolam 1.28+.57, thiopental 2.54+.68, and isoflurane 3.6+.59. (See figure) Damage was significantly less in the midazolam group compared to control (p=.03). The thiopental and ketamine groups each had one rat with minimal subsantia nigra damage, although the average extent of damage in each group as a whole was not significantly different from the control group. Damage in the isoflurane group was not different compared to the control group.

Discussion: Our data show control of seizure activity by each anesthetic tested. The data further suggest that some anesthetics, administered after seizures are stopped, may be able to protect the brain during a postictal vulnerable period. This effect is particularly suggested with midazolam and to lesser extent with thiopental and ketamine. Finally, although it is quite effective at stopping seizures, we find no neuropathologic advantage with isoflurane used to stop seizures. Supported by the Puritan-Bennett Foundation.

References:

1. Delgado-Escueta AV, Wasterlain C, Treiman DM, Porter RJ, Management of Status Epilepticus. N Eng J Med, 306:1337-1340, 1982